IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BJORSNE et al

Atty. Ref.: 3525-95

Serial No. 09/623,705

Group: 1625

Filed: September 7, 2000

Examiner: Robinson, B.

For: NEW BISPIDINE COMPOUNDS USEFUL IN THE TREATMENT OF CARDIAC ARRYTHMIAS

#19
Cancel
1-15-03

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November 25, 2002

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

RESPONSE

This is in response to the Official Action mailed August 27, 2002.

Reconsideration is respectfully requested. Claims 1-13 and 19-27 are in the case.

I. CLAIMS 15 AND 16

The Examiner has objected to Claim 15 and 16. Those claims were canceled in the Amendment dated May 13, 2002.

II. THE 35 U.S.C. 112, SECOND PARAGRAPH, REJECTION

Claims 1, 3-13, 19 and 20 (in part) stand rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for the reasons discussed on page 3 of the action. That rejection is respectfully traversed.

In subparagraph A, Claim 20 has again been rejected on the ground that the term "derivative" is allegedly indefinite. No reasoning is given. In the prior action, the Examiner asserted that it is "unclear as to the compounds being claimed."

It is again noted that claim 20 relates to a **process** for preparing compounds of formula I, and does not claim any compounds. Moreover, while the Examiner has not specified which part of Claim 20 the objection is raised against, it is assumed that part (u) (which mentions a "protected derivative" of a compound of formula I) is the section referred to by the Examiner. Clarification in this regard from the Examiner is again respectfully requested.

If the Examiner's objection is directed to part (u) of Claim 20, it is noted that "protected derivative" is language which would have been completely clear to one of ordinary skill in this art as of the filing date of the case. A person of ordinary skill would have appreciated that a protected derivative of a compound of Formula I will be a compound that can be converted, in a simple deprotection step, to a compound of formula I. Moreover, the person of ordinary skill would have been well aware of a large number of protective groups which may be used to protect the functional groups present in compounds of formula I (such as protective groups disclosed in the books mentioned at page 37, lines 5-8 of the application as originally filed).

Should Applicants be forced to specify exact structures of the protected compounds used in step (u) of Claim 20, the claim would no longer provide the proper protection for this invention. That is, in hindsight of the disclosure of the invention, it would be a trivial matter for one of ordinary skill to use any given protective group in the process of part (u) of original Claim 20, thus making it easy for one of ordinary skill to avoid the claim if it is limited with respect to the structure of the protected derivative. Withdrawal of this aspect of the formal rejection is accordingly respectfully requested.

In subparagraph C, claim 1, lines 4-6 and other occurrences in claims 3-20 has again been objected to in light of the language "optionally substituted and/or terminated (as appropriate)". In response, it is pointed out that the claims were amended in the prior response to delete "and/or terminated (as appropriate)." Withdrawal of this aspect of the formal rejection is accordingly respectfully requested.

In subparagraph D, claim 1, lines 22 and 23 and other occurrences throughout claims 3-20 have again been rejected in regard to the phrase "(which latter three groups..)" is allegedly indefinite. It is not understood why the Examiner persists with this objection. It is clear that, for example, the term "which latter three groups" refers to the last three groups that have been previously mentioned. In the example cited by the Examiner, it is therefore clear from the wording of the application as filed that, for the group "A":

(i) the $-(CH_2)_m-$group of $-N(R^{25})(CH_2)_m-$, $-O(CH_2)_m-$ or $-(CH_2)_mC(H)(OR^{25})(CH_2)_n-$ is attached to the bispidine N-atom; and

(ii) each of C_{1-6} alkyl, $-N(R^{25})(CH_2)_m-$, $-O(CH_2)_m-$ or $-(CH_2)_mC(H)(OR^{25})(CH_2)_n-$ is optionally substituted by one or more OH groups.

The above facts are clearly expressed in claim 1 as presently worded. It is not seen how this definitional language can be presented in a form which is clearer than this. The alternative wording suggested by the Examiner appears to be considerably less clear. That is, it appears that the Examiner is suggesting recasting the definition of "A" such that it reads :

> A is $-NR^{25})(CH_2)_m-$, $-O(CH_2)_m-$ or $-(CH_2)_mC(H)(OR^{25})(CH_2)_n-$, or C_{1-6} alkyl, $-N(R^{25})(CH_2)_m-$, $-O(CH_2)_m-$ and $-(CH_2)_mC(H)(OR^{25})(CH_2)_n-$ which are optionally substituted with one or more OH groups, or $-N(R^{25})(CH_2)_m-$, $-O(CH_2)_m-$ and $-(CH_2)_mC(H)(OR^{25})(CH_2)_n-$ which are attached to the bispidine nitrogen...".

Apart from the fact that this definition is repetitious, it is unclear (for example in the situation that "A" can represent more than one group). Moreover, it does not appear to describe the same subject matter as described by the current definition of "A". Reconsideration is respectfully requested.

In subparagraph E, claim 11 has been objected to in regard to the phrase "in which latter two cases p is 1, 2 or 3)" is allegedly indefinite. Again, it is not understood how the use of the word "latter" gives rise to any lack of clarity. The wording of claim 11 is perfectly clear and precise in specifying that, when B represents $-(CH_2)_pO-$ or $-(CH_2)_pN(R^{26})-$, p is 1, 2 or 3. Moreover, should "in which latter two cases" be replaced by "wherein," there would be ambiguity as to whether the restricted definition of "p" applied to $-(CH_2)_pN(R^{26})-$ alone or to both $-(CH_2)_pO-$ and $-(CH_2)_pN(R^{26})-$. Claim 1 as presently worded is believed to be clear. Reconsideration of this aspect of the formal rejection is respectfully requested.

IV. THE OBVIOUSNESS REJECTION

Claims 1 and 3-13, 19 and 20 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over EP 0308843 to Lubisch et al. That rejection is respectfully traversed.

Attention is directed to the proviso (a) and (b) at page 58, lines 19-21 of the application as filed. As a result of those provisos, all of the compounds of claim 1 bear a C_{1-3} alkyl substituent in one or more of the 2-, 4-, 6-, and 8-positions of the bispidine ring.

EP 308843 describes only compounds that are **unsubstituted** at those positions. Moreover, the compounds of claim 1 are all carbamates or thiocarbamates (due to the presence of the $C(O)XR^1$ group). EP 308843 describes solely amide and urea compounds (see the definition of the group "Y," which represents C(O) or C(O)NH only).

Thus, the compounds of Lubisch differ from the compounds of the present invention in that:

(i) neither the group *"Y"* nor the group "*Z*" of the compounds of Lubisch can represent the essential -C(O)X- group of the compounds of the present case; and

(ii) the compounds of Lubisch are unsubstituted at the 1, 2, 4, 5, 6 and 8-positions of the 3,7-diazabicyclo[3.3.1]nonane ring. This contrasts with the compounds of the present case which carry a C_{1-3} alkyl group at a minimum of one of these ring-positions.

In light of the above, it is clear that EP 308843 does not disclose or suggest the compounds as claimed in Claim 1. There would have been no motivation for one of ordinary skill to resort to that disclosure in the context of the presently claimed invention. Even if that did occur, it is clear that the presently claimed invention would not have

resulted or have been rendered obvious thereby. Reconsideration and withdrawal of the outstanding obviousness rejection based on Lubisch et al are accordingly respectfully requested.

V. THE 35 U.S.C. 112, FIRST PARAGRAPH, REJECTION

Claims 1 and 3-13, 19 and 20 stand rejected under rejected under 35 U.S.C. 112, firest paragraph, on alleged lack of enablement grounds. The rejection is respectfully traversed.

It is not understood which definitions the Examiner believes are not fully enabled. The reason for this is that it is unclear which groups the definitions mentioned by the Examiner actually belong to.

It is possible that the Examiner believes that the following definitions are not enabled:

(a) R^1 represents $-(CH_2)_a$-Het^1 (optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

(b) R^9 represents $-(CH_2)_a$-Het^1 (optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)R^{13}$, $C(O)OR^{14}$ and/or $N(H)S(O)_eR^{15}$); and

(c) R^{14} and R^{15} independently represent aryl or $-(CH_2)_k$-aryl (optionally substituted by one or more substituents chosen from halo, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy).

The Examiner also alleges that certain other definitions (relating to Het^2, Het^3 and A) are not fully enabled. However, the explanation in relation to these definitions is so

unclear that the objection cannot be understood. It is requested that the Examiner clarify exactly those definitions to which the rejection applies. The objections appear to be based on an alleged lack of exemplification of the relevant definitions. However, the Examiner has not provided any basis as to why one skilled in the art would be unable to prepare and use all of the compounds falling within the scope of the claims. In this respect, attention is directed to the specification where copious information relating to the synthesis and use of the compounds of the invention (including compounds possessing substituents that have the definitions objected to) is provided (see page 11 to page 52 of the application as filed).

At the bottom of page *5* of the Action, the Examiner has stated:

> "Heteroaryl or aryl rings cannot support electron-withdrawing groups such as cyano or nitro in the ortho or meta position..."

If this statement is given its plain meaning (i.e. that it is not possible to make compounds that possess heteroaryl or aryl groups with such substitution patterns), then it has no basis in fact whatsoever. For example, commercially available phthalonitrile is a compound in which a benzene nucleus is substituted by two cyano groups that are *ortho* relative to each other. Moreover, there are countless other known compounds having the substitution patterns that the Examiner alleges cannot be supported. Clarification is respectfully requested.

Reconsideration of the lack of enablement rejection is believed to be in order. Such action is respectfully requested.

VI. INFORMATION DISCLOSURE STATEMENT

In relation to point 9 of the Office Action, it is noted that the only European patents cited in the International Search Report are EP 306 871 and EP 308 843 (Lubisch). There is no citation of EP 308 848.

Attached to the previous response was a completed PTO-1449 listing U.S. Patent No. 6,291,475, together with a copy of that patent and the requisite IDS check ($180.00). The Examiner is requested to initial that PTO-1449 and to return a copy of the initialed document to the undersigned with the next paper to issue in this application.

It is noted that the Examiner has not acknowledged the IDS dated August 30, 2001. The Examiner is requested to acknowledge receipt of that document and return a copy of the initialed PTO-1449 to the undersigned with the next paper to issue in this application.

Allowance of the application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

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